

3.1 Technical Abstract

The clinical study is a Phase 1 trial to evaluate recombinant DNA and adenovirus expressing the L523S protein (pVAX/L523S and Ad/L523S, respectively) in patients with early, non-small cell lung cancer (NSCLC). The primary objective of this trial is to determine the safety of a vaccine regimen consisting of two fixed priming doses of pVAX/L523S followed by two boosting doses of Ad/L523S with dose-escalation through three cohorts in patients with early NSCLC who have undergone primary surgical resection of the lung tumor within the previous three years. Additionally, this trial will assess the extent to which antibody and/or cell-mediated immunity (CD4+ and/or CD8+) specific for the L523S protein will be elicited by this vaccine regimen.

The L523S DNA-Adenovirus Immunotherapeutic vaccine targets a lung cancer-associated protein in order to prevent recurrence. The immunogenic protein is termed L523S. The vaccine product contains two components, plasmid DNA containing the L523S gene (pVAX/L523S) and a recombinant adenovirus-5 containing the L523S gene (Ad/L523S). pVAX/L523S is designed to initiate and stimulate (prime) an immune response to the L523S protein, which is found to be highly expressed in lung carcinomas. Ad/L523S, expressing the L523S immunogenic protein, will be used to expand and enhance (boost) the effectiveness of the response to pVAX/L523S administration.

The rationale for the use of both DNA and adenovirus as immunizing agents is based on their proven ability to elicit strong cell-mediated responses, particularly cytotoxic T lymphocytes (CTL) to recombinant antigens (1). Administering DNA first is expected to generate an initial weak immune response sufficient to prime CD4+ and CD8+ lymphocyte populations recognizing L523S epitopes. The subsequent administration of an adenovirus construct containing the L523S gene is expected to boost the initial immune response by favoring the expansion of primed CD4+ and CD8+ T cells. Priming with DNA and subsequent boosting with recombinant adenovirus, or other recombinant viruses, has already been found to be an effective method to generate a powerful humoral and cellular immune response (1-4).

The proposed clinical protocol is a Phase 1 open-label, safety and immunogenicity study of a fixed dose of pVAX/L523S followed by ascending doses of Ad/L523S, in three cohorts of patients with Stage IB or II non-small cell lung cancer who have undergone primary surgical resection of the lung tumor within the previous three years. The pVAX/L523S and Ad/L523S will be administered separately by intramuscular (IM.) injection at separate time points. In the proposed clinical study, immunization with pVAX/L523S will use the Bioject needle-free delivery system (Biojector[®] 2000) and Ad/L523S will be administered using standard needle and syringe injections.

Three to six cancer patients will be enrolled in each of three cohorts in the study. All patients will initially receive two 1.0 mL IM injections of 4 mg pVAX/L523S (total of 8 mg DNA) at baseline (Day 0) and at Day 14. The first group of patients, after completion of the pVAX/L523S injections, will receive 1×10^9 viral particles of Ad/L523S by IM injection in the lateral deltoid muscles at Day 28 and at Day 56. Doses of Ad/L523S will be escalated in the subsequent cohorts to 2×10^{10} and 2×10^{11} viral particles, respectively.

1. Shiver JW, Fu TM, Chen L, et al. Replication-incompetent adenoviral vector elicits effective anti-immunodeficiency-virus immunity. *Nature*. 2002;415:331-335.
2. Allen TM, Vogel TU, Fuller DH, et al. Induction of AIDS virus-specific CTL activity in fresh, unstimulated peripheral blood lymphocytes from rhesus macaques vaccinated with a DNA prime/modified vaccinia virus Ankara boost regimen. *J Immunol*. 2000;164:4968-4978.
3. Amara RR, Villinger F, Altman JD, et al. Control of a mucosal challenge and prevention of AIDS by a multiprotein DNA/MVA vaccine. *Science*. 2001;292:69-74.
4. Estcourt MJ, Ramsay AJ, Brooks A, Thomson SA, Medveckzy CJ, Ramshaw IA. Prime-boost immunization generates a high frequency, high avidity CD8+ cytotoxic T lymphocyte population. *Int Immunol*. 2002;14:31-37.